

REMARKS

*1. Claim Objections*

Claim 2 is objected to because "epithelial" is misspelled. Applicant has amended the claim to correct the misspelling and kindly request that this informal objection be withdrawn.

*2. Claim Rejections – 35 USC § 112, Second Paragraph*

Claims 3, 6, 7, 9, 11, 13, 16, 17, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. In order to expedite prosecution and advance this application to issuance, Applicant has amended claims 3, 6, 11, 13, 16 and 19-20. In light of these amendments applicant believes this rejection is now moot and kindly requests its withdrawal.

Claims 3 and 13 recite an antibody or fragment directly or indirectly attached to a detectable label.

The Office Action asserts that the disclosure fails to teach the meaning of indirect attachment of the detectable labels and thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite. Applicant respectfully traverses. Applicant contends that a person of skill in the relevant art would understand that the detectable label could be attached to the antibody either directly or indirectly (i.e., by use of an appropriate linker) and that this knowledge is well within the scope of someone skilled in the relevant art and so being. However, in order to promote prosecution and advance the case to issue, Applicant has amended claims 3 and 13 to remove the word "indirectly" thereby rendering this rejection moot.

Claims 6, 7, 16 and 17 recite the limitation "the intestinal tissue" in line 2 or 3 of each of the claims.

The Office Action asserts that there is insufficient antecedent basis for this limitation in the claims because the base claims from which the claims depend recite gastric tissue, not intestinal tissue. Applicant has amended claims 6, upon which 7 relies, and 16, upon which 17 relies, to substitute the words "gastric" for "intestinal" thereby rendering this informal rejection moot.

Claims 9 and 19 recite performing a further step of performing a negative control assay on a negative control sample to detect human gastric intestinal metaplasia cells present in the negative control sample.

The Office Action asserts that the methods of the base claims are drawn to detecting gastric intestinal metaplasia cells in a gastric tissue sample as a positive indication of disease, i.e., the presence of the cells indicates that the sample is positive. It is therefore unclear how a sample in which positive cells are detected can function as a negative control.

Applicant respectfully traverses. Applicant contends that a person skilled in the relevant art, upon reading the claim in light of the specification, especially page 15, lines 35-39, would understand that the negative control assay is to be performed on cells that do not contain the human gastric intestinal metaplasia antigen and that this assay would establish a negative control, whereby when the results of this assay are compared to the results of those of the base claim, any results above that obtained in the negative control assay would be a positive indicator of human gastric intestinal metaplasia of the colonic phenotype. In view of this, Applicant contends that claims 9 and 19 are clear and distinct as written.

Claim 11 is drawn to an immunoassay method for screening for human gastric intestinal metaplasia, thereby indicating a predisposition for gastric carcinoma.

The Office Action asserts that it is unclear whether diagnosis of human gastric intestinal metaplasia is in and of itself indicative of a predisposition for gastric carcinoma or whether the indication of the predisposition is dependent upon immunoreactivity with monoclonal antibody DAS- 1. Applicant respectfully traverses. Applicant contends that a person of skill in the relevant art would understand that in light of the specification, specifically page 7, lines 9-36 and page 21, line 15 to page 22, line 33, that the monoclonal antibody DAS-1 reacted with 35% of gastric intestinal metaplasia samples without gastric carcinoma and reacted with 94% of gastric intestinal metaplasia samples with gastric carcinoma thereby indicating that although human gastric metaplasia may transform into intestinal type gastric cancer, this may not always be the case, but that reactivity with the DAS-1 monoclonal antibody is indicative of an increased risk of contracting gastric carcinoma. In view of this Applicant contends that claim 11 is clear and distinct as written. However, in order to expedite prosecution and advance the case to issuance, Applicant has amended claim 11 to more clearly point out the subject matter of the claimed invention.

### ***3. Claim Rejections – 35 USC § 112, First Paragraph***

#### **a. Rejection of claims 1-20**

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Office Action asserts based on factors such as the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance

present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed, that claims 1-20 are not enabled because the specification does not meet the enablement requirement of 35 U. S.C. 112, first paragraph and that undue experimentation would be required.

The Office Action, rejects claims 1-20 under 35 U.S.C. 112, first paragraph, for not being enabled by the specification “for diagnosing other gastric intestinal metaplasias.” See page 4 of the Office Action. While Applicant agrees with the Examiner that the specification is enabling for “diagnosing human gastric intestinal metaplasia of the incomplete or colonic type,” Applicant respectfully traverses the enablement rejection. Applicant contends that the specification shows that there are several phenotypic changes, including gastric intestinal metaplasia, that occur in the cascade of events that eventually leads from normal mucosa to intestinal-type gastric cancer. See page 2, lines 35-38. The specification states that histologically confirmed gastric intestinal metaplasia specimens from two institutions were examined (page 7, lines 20-22) and that the DAS-1 antibody reacted to varying degrees with a colonic phenotype of gastric intestinal metaplasia. (page 7, lines 32-36). Hence, the specification shows that the DAS-1 antibody reacts with the intestinal metaplasia antigen (that is the colon epithelial specific protein) that is found in 35% of gastric intestinal metaplasia cells that do not test positive for gastric carcinoma (i.e., cells which are displaying the colon epithelial specific protein) and 94% of gastric intestinal metaplasia cells that do test positive for gastric carcinoma, thereby showing that not only is the DAS-1 antibody an indicator of gastric intestinal metaplasia, as shown by Example 1 (page 7, lines 20-36), but also that it is a good indicator for the potential of a gastric intestinal metaplasia cell’s conversion into a gastric carcinoma cell.

However, in order to expedite prosecution and advance the case to issuance, Applicant has amended claims 1, 3, 6, 9-13, 16, 19 and 20. Applicant respectfully submits that the claims, as amended, are deemed by the Examiner to be enabled by the specification. Claims 1-10 are now directed to a method for diagnosing human gastric intestinal metaplasia of the colonic phenotype and claims 11-20 are directed to a method for diagnosing a predisposition for gastric carcinoma. Applicant therefore believes this rejection is now moot and respectfully request it be withdrawn.

**b. Rejection of claims 6-8 and 16-20**

Claims 6-8 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action asserts that the example in the specification is drawn to immunoreactivity of DAS-1 with gastric tissue samples, not intestinal tissue samples, as diagnostic of incomplete or colonic gastric intestinal metaplasia (pages 21-22) and hence, one of skill in the art would be unable to practice the claimed invention, which is drawn to immunoperoxidase staining of intestinal tissue with the monoclonal antibody DAS- 1 in order to diagnose gastric intestinal metaplasia, absent undue experimentation.

In order to expedite prosecution and advance issuance, Applicant has amended claims 6 and 16 to recite “gastric” tissue instead of “intestinal” tissue. Applicant contends that claims 6 and 16 now conform with claims 1 and 11, up on which they depend, which both recite “gastric tissue” and therefore this rejection is now moot. In light of these amendments, applicant kindly request the rejection be reconsidered and withdrawn.

**c. Further rejection of claims 1-20**

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action asserts that the specification lacks complete deposit information for the deposit of the hybridoma ATCC accession number HB 9397. While the specification provides enough information for one of skill in the art to produce a hybridoma with the same or similar properties as hybridoma ATCC accession number HB 9397, reproduction of an identical hybridoma is an unpredictable event. Because the claims specially require the use of the monoclonal antibody DAS-1 produced by hybridoma ATCC accession number HB 9397, evidence must be provided that hybridoma ATCC accession number HB 9397 is readily available to the public. It is not clear from the disclosure that deposits of hybridoma ATCC accession number HB 9397 meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath.

Pursuant to the Examiner's request, an affidavit signed by the named inventor, addressing all the points raised in the Office Action, is here with filed. In light of this affidavit, Applicant believes this rejection is now moot and kindly requests its withdrawal.

**4. Claim Rejections – 35 USC § 102**

a. Claims 1, 3-5, 9-11 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Garewal et al. (Gastroenterology 112 (4 SUPPL.):pA567, 1997)

The Office Action asserts that the claimed invention is drawn to a method of diagnosing human gastric intestinal metaplasia comprising contacting a gastric tissue sample with the monoclonal antibody DAS-1 and detecting immunoreactivity; wherein the antibody is attached to a detectable label and wherein immunoreactivity in the sample indicates a predisposition for gastric carcinoma in the patient. The Office Action asserts that Garewal et al. teach a method for detecting an incomplete type of gastric intestinal metaplasia comprising staining gastric cardia biopsy tissues by immunoperoxidase using monoclonal antibody DAS-1 and staining normal gastric cardia tissue and samples showing gastric intestinal metaplasia as a negative and positive controls. Lastly, the Office Action asserts that Garewal et al. teach that the incomplete gastric intestinal metaplasia they analyzed was the type that is associated with gastric adenocarcinoma.

To the extent that the rejection can be held to apply to the claims as amended, Applicant respectfully traverses. In order for a cited reference to anticipate a claimed invention a cited reference must describe each and every element of the claim. Garewal et al. teaches that DAS-1 reacts with Barrett's Esophagus tissue but not with normal esophageal mucosa, the gastroesophageal junction, or other different parts of the stomach or small intestine. The study used gastric cardia biopsies to ascertain the frequency of reactivity with DAS-1 to delineate with which type of intestinal mucosa DAS-1 reacts. Toward this purpose, 19 biopsies were taken, 10 from normal appearing gastric mucosa (which proved negative for DAS-1 staining) and 9 that revealed metaplasia, four of which revealed positive reactivity (staining) for DAS-1. These staining patterns were then compared to that of Alcian Blue/High Iron Diamine staining. The results showed first, that DAS-1 reacts with a subset of intestinal metaplasia of the cardia (that associated with gastric adenocarcinoma) and that DAS-1 was as effective in differentiating the

different types of gastric intestinal metaplasia as Alcian Blue/High Iron Diamine, but easier to use because only one staining procedure need be carried out.

The present invention, as amended, is directed to a method for diagnosing gastric intestinal metaplasia of the colonic phenotype that involves contacting a gastric tissue sample with the DAS-1 antibody that reacts with the human gastric intestinal metaplasia antigen. Garewal et al. therefore teaches the use of the DAS-1 monoclonal antibody, to diagnose a different type of cancer, by its reaction with a different type of tissue. The gastric cardia biopsies of Garewal et al. were from esophageal tissue, which was taken from the opening of the esophagus into the stomach. The colonic gastric intestinal metaplasia of the present invention involves gastric tissue that is histologically different from the tissue used in Graewal et al. Furthermore, the claims of the present invention require reactivity of the DAS-1 antibody with the human intestinal metaplasia antigen, the Graewal et al. reference neither mentions nor describes such a limitation. Because each and every limitation of the claims is not described by the Graewal et al. reference, that reference can not anticipate the present invention. In light of the amendments, Applicant kindly requests the Examiner reconsider and withdraw the rejection.

b. Claims 1-5 and 9-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Griffel et al.

The Office Action asserts that Griffel et al. teach a method for diagnosing Barrett's esophagus by immunoperoxidase staining comprising contacting gastric cardia biopsy tissue with the monoclonal antibody DAS- 1, which reacts with colonic epithelial specific protein, and rabbit anti-mouse antibody conjugated to peroxidase and that the monoclonal antibody is immunoreactive with the colonic type of intestinal metaplasia but not with normal gastric tissue. Griffel et al. teach staining biopsy samples taken from cases of histologically confirmed Barrett's



esophagus and from samples of normal morphology without intestinal metaplasia as positive and negative controls.

To the extent that this application can be held to apply to the claims as amended, Applicant respectfully traverses. Griffel et al. teaches that monoclonal antibody DAS-1 recognizes specialized columnar epithelium (SCE) in the esophagus, thereby showing that DAS-1 may be used as a diagnostic for Barrett's Esophagus. The interesting point about this study was that it determined that the DAS-1 monoclonal antibody could be used to detect the phenotypic change of the gastroesophageal junction epithelia to a colonic cell type prior to morphological change and that it was shown that DAS-1 also recognized metaplastic samples in the absence of histological evidence of specialized columnar epithelium. This last point goes to show that Barrett's Esophagus may occur in the absence of SCE.

In this study 52 specimens from the distal esophagus were biopsied, using labeled DAS-1, and 54 cardia-type mucosa specimens from the stomach were biopsied, as controls. The staining patterns were compared with Alcian blue/high iron diamine (AB/HID). The results indicated that both DAS-1 and AB/HID reacted with 10 samples diagnosed to have SCE, while DAS-1 further reacted with an additional 5 samples that were not diagnosed as having SCE.

Although, Griffel et al. showed that DAS-1 reacts with colonic intestinal epithelium, it did not, however, show that DAS-1 could react with gastric metaplastic tissue and that this could be a diagnostic for the risk of gastric carcinoma. Rather it simply showed that esophageal tissue goes through a morphological change as it progresses toward Barrett's Esophagus, whereby DAS-1 can be used to distinguish the terminal stage in this progression. Hence, the purpose of Griffel was to show a diagnostic for Barrett's Esophagus, in which esophageal tissue is biopsied to test reactivity with DAS-1. As stated above, the gastric intestinal metaplasia of the present

invention involves gastric tissue, which is histologically different from the tissue used in Griffel et al, and furthermore, the claims of the present invention require reactivity of the DAS-1 antibody with the human intestinal metaplasia antigen, that the Griffel et al. reference neither mentions nor describes.

#### 5. *Claim Rejections – 35 USC § 103*

a. Claims 2-and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garewal et al. in view of Badve et al. (Hepatology 28/4:523A, Nov. 1998).


The Office Action asserts that the claimed invention is drawn to a method of diagnosing human gastric intestinal metaplasia comprising contacting a gastric tissue sample with the monoclonal antibody DAS-1, which reacts with colonic epithelial specific protein, and detecting immunoreactivity, wherein immunoreactivity in the sample indicates a predisposition for gastric carcinoma in the patient.

The Office Action asserts that Garewal et al. teach diagnosing incomplete type of gastric intestinal metaplasia by staining gastric cardia biopsy tissues using immunoperoxidase with monoclonal antibody DAS- 1, but that Garewal does not teach the specific antigen present in the tissue with which the monoclonal antibody reacts. The Office Action asserts that Badve et al. teach that monoclonal antibody DAS-1 is immunoreactive with a specific colonic epithelial protein. Hence, the Office Action asserts that one of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to have stained a gastric tissue sample for colonic epithelial specific protein as diagnostic of incomplete type of gastric intestinal metaplasia because Garewal et al. teach that the antibody is diagnostic of incomplete type of

gastric intestinal metaplasia and Badve et al. teach that the specific immunoreactivity of the antibody is to a specific protein in the colonic epithelium.

To the extent that the rejection can be held to apply to the claims as amended, Applicant respectfully traverses. Applicant contends that these references do not teach nor suggest all the elements of the claimed invention. As stated above, Garewal et al. teaches that DAS-1 is reactive with Barrett's Esophagus. Gastric cardia concerns esophageal tissue, which was taken from the opening of the esophagus into the stomach, this tissue is histologically different from the gastric tissue of the present invention. Gastric cardia tissue behaves like the esophagus and not like the tissue of the digestive track (i.e., the stomach or intestines).

Further, Applicant contends that it would not have been obvious to use the methods taught by Garewal of using DAS-1 for diagnosing human gastric intestinal metaplasia especially that of the colonic phenotype because prior art teaches that DAS-1 does not react with normal tissue of the small intestine, tissue that is more closely related to that of the colon than the esophagus. *Das et al.*, J. Immunol. 139:77, 1987. Further still, prior art actually teaches away from the notion that DAS-1 would be reactive with gastric tissue and be predictive of gastric cancer in that squamous cell carcinoma of the esophagus does not react to DAS-1 while Barrett epithelium and adenocarcinomas arising from Barrett's epithelium do (see *Das et al.*, Annals of Internal Medicine 120(9): 753-756)). Hence, one skilled in the art would not have expected that because DAS-1 reacts with Barrett's Esophagus that it would react with small intestine or colonic metaplasia tissue and be predictive of gastric carcinoma, especially in light of the fact that it doesn't react with squamous cell carcinoma of the esophagus. In light of this, Applicant contends the references, either alone or in combination, do not teach all of the elements of the claimed invention, and therefore, respectfully requests the rejection be withdrawn.



b. Claims 1-6, 8-16, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Garewal et al. in view of Badve et al., or Griffel et al., as applied to claims 1-5 and 9-15 above, and further in view of Pantuck et al. (British Journal of Urology 82:426-430), Babaev et al. (Database Medline on Dialog, 03905999, Arkhiv Patoly.i, 45/1:76-78, 1983), and Petersen et al. (Database Medline on Dialog, 05813907, Journal of Histochemistry and Cytochemistry, 34/6:801-809, June 1986).

The Office Action asserts that the claimed invention is drawn to a method of diagnosing human gastric intestinal metaplasia comprising contacting a gastric tissue sample with the monoclonal antibody DAS-1, which reacts with colonic epithelial specific protein and detecting immunoreactivity; wherein the antibody is attached to a detectable label; wherein the detecting is performed by a method selected from the immunoperoxidase stain, among others; wherein positive and negative controls are run with the method; and wherein immunoreactivity in the sample indicates a predisposition for gastric carcinoma in the patient.

The Office Action asserts that either of Garewal et al. in view of Badve et al., or Griffel et al., teach a method for staining gastric biopsy tissue by immunoperoxidase using the monoclonal antibody DAS-1 and an anti-mouse antibody conjugated to peroxidase for diagnosis of the colonic type of intestinal metaplasia. The Office Action asserts that Griffel et al. teaches heating the slides; rehydrating the slides with xylene and decreasing concentrations of alcohol at 100% and 80%; washing in PBS; contacting the slides with NaBH<sub>4</sub>; reacting the tissue with the monoclonal antibody, an anti-mouse antibody conjugated to biotin, and streptavidin peroxidase; treating with diaminobenzidine, washing, and staining with H&E (see the paragraph bridging pages 41 and 42). The Office Action admits that neither Garewal et al. in view of Badve et al.

nor Griffel et al. teach reacting the tissue with normal goat serum, incubating with a goat anti-mouse antibody, or a graded alcohol series of 100%, 95%, 70%, and 50% for rehydration.

However, the Office Action does assert that Pantuck et al. teach a method of staining paraffin-embedded tissue specimens with the monoclonal antibody 7E12H12 (which the specification teaches is an alternative name for DAS-1; see page 7, line 14) comprising heating the slides to deparaffinize the tissue, immersing the slides in xylene; rehydrating the slides with decreasing concentrations of alcohol at 100%, 95%, and 80%; washing in PBS; reducing the free aldehydes with NaBH<sub>4</sub>; reacting the tissue with the monoclonal antibody, an anti-mouse antibody conjugated to biotin, and streptavidin peroxidase; treating with diaminobenzidine, washing, and staining with H&E (see the paragraph bridging pages 41 and 42) and that Babaev et al. teach that incubation of paraffin sections with normal goat serum decreases nonspecific staining and Petersen et al. teach goat anti-mouse antibody conjugated to peroxidase as the secondary antibody in an immunoperoxidase staining method.

Hence, the Office Action asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used normal goat serum to reduce nonspecific staining in the method taught by either Garewal et al. in view of Badve et al. or Griffel et al. for reduction of nonspecific staining and to have used goat anti-mouse antibody as the secondary antibody in the method of Garewal in view of Badve et al. or as an equivalent of the rabbit anti-mouse antibody disclosed by Griffel et al.

The Office action asserts that one of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to have rehydrated the tissue in decreasing concentrations of alcohol, as is taught by Pantuck et al. Further, although Pantuck et al. teach 100%, 95%, and 80% as the gradient alcohol solutions, absent some evidence to the contrary, the

claimed gradients of 100%, 95%, 70% and 50% would be considered as equivalent to those of Pantuck et al.

Applicant respectfully traverses to the extent that this rejection can be held to apply to the claims as amended. Again, as stated above, Applicant contends that these references do not teach nor suggest all the elements of the claimed invention. Neither Garewal et al. nor Griffel et al. teaches a method for diagnosing human colonic type gastric intestinal metaplasia, nor that this reactivity can be predictive of gastric carcinoma. Rather both Garewal and Griffel teach that DAS-1 is reactive with Barrett's Esophagus. As stated above, gastric cardia concerns esophageal tissue, which was taken from the opening of the esophagus into the stomach. This tissue is histologically different from the tissue of the gastric tissue of the present invention, especially in light of the fact that gastric cardia tissue behaves like the esophagus and not like the tissue of the digestive track (i.e., the stomach or intestines).

Further, as stated above, Applicant contends that it would not have been obvious to use the methods taught by Garewal or Griffel for using DAS-1 for diagnosing human gastric intestinal metaplasia, especially of the colonic phenotype, because prior art actually teaches away from the notion that DAS-1 would be reactive with gastric tissue and that it could be predictive of gastric cancer. First of all, prior art teaches that DAS-1 does not react with the tissue of the small intestine, tissue that is more closely related to that of the colon than the esophagus. *Das et al.*, J. Immunol. 139:77, 1987. Further still, although Barrett's Esophagus tissue does react to DAS-1 (see U.S. Patent No. 5,888,743 to Das), the prior art teaches that squamous cell carcinoma of the esophagus does not react to DAS-1. Hence, one skilled in the art would not have expected that because DAS-1 reacts with Barrett's Esophagus, as described in Garewal and Griffel, that it would react with gastric metaplasia tissue and be predictive of gastric carcinoma,

especially in light of the fact that it doesn't react with squamous cell carcinoma of the esophagus. In light of this, Applicant contends the references, either alone or in combination, do not teach all of the elements of the claimed invention, and even if they did, there would be no motivation to combine them because prior art actually teaches away from this, hence, Applicant respectfully requests the rejection be withdrawn.

c. Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Garewal et al. and Badve et al., or Griffel et al., in view of Pantuck et al., Babaev et al., and Petersen et al. as applied to claims 1-6, 8-16, and 18-20 above and further in view of Pinkus et al. (Database Medline on Dialog, 06042776, Journal of Histochemistry and Cytochemistry, 33/5:465-473, May 1985).

The Office Action asserts that the claimed method, described above, further comprises trypsinizing the tissue before reacting the tissue with the goat serum and monoclonal antibody. The Office Action admits that none of Garewal et al., Badve et al., Griffel et al., Pantuck et al., Babaev et al., or Petersen et al. teach reacting the tissue with trypsin prior to addition of the antibodies. However, the Office Action asserts that Pinkus et al. teach that preliminary trypsinization of formalin-fixed paraffin-embedded tissues ensures optimal reactivity of monoclonal antibodies with the target antigens in immunoperoxidase techniques.

Hence, the Office Action asserts that one of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to have added a trypsinization step to the method of either Garewal et al. and Badve et al., or Griffel et al., in view of Pantuck et al., Babaev et al., and Petersen et al., as taught by Pinkus et al., in order to ensure optimal reactivity of the DAS-1 monoclonal antibody with the target antigen in paraffin-embedded gastric tissue.

Applicant respectfully traverses to the extent that this rejection can be held to apply to the claims as amended. Again, as stated with reference to the other 103 rejections, Applicant contends that the references cited therein do not teach nor suggest all the elements of the claimed invention as amended. Specifically, neither Garewal et al. nor Griffel teach a method for diagnosing human colonic type gastric intestinal metaplasia, nor that this reactivity can be predictive of gastric carcinoma. Rather, both Garewal and Griffel teach that DAS-1 is reactive with Barrett's Esophagus tissue, and as previously stated, gastric cardia concerns esophagus tissue, which was taken from the opening of the esophagus into the stomach. This tissue is histologically different from the tissue of the gastric tissue of the present invention, especially in light of the fact that gastric cardia tissue behaves like the esophagus and not like the tissue of the digestive track (i.e., the stomach or intestines).

Further, as stated above, Applicant contends that it would not have been obvious to use the methods taught by Garewal or Griffel for using DAS-1 for diagnosing human gastric intestinal metaplasia, because prior art actually teaches away from the notion that DAS-1 would be reactive with gastric tissue and that it could be predictive of gastric cancer. First of all, prior art teaches that DAS-1 does not react with the tissue of the small intestine, tissue that is more closely related to that of the small intestine and colon than the esophagus. *Das et al.*, J. Immunol. 139:77, 1987. Further still, although Barrett's Esophagus tissue does react to DAS-1 (see U.S. Patent No. 5,888,743 to Das), the prior art teaches that squamous cell carcinoma of the esophagus does not stain for DAS-1. Hence, one skilled in the art would not have expected that because DAS-1 reacts with Barrett's Esophagus, as described in Garewal and Griffel, that it would react with gastric intestinal metaplasia tissue and be predictive of gastric carcinoma, especially in light of the fact that it doesn't react with squamous cell carcinoma of the esophagus.



Id. Because of this there would be no motivation to combine the references in the manner suggested by the Office Action, and even if such a combination were made, the instant invention could not be derived. In light of this, Applicant contends the references, either alone or in combination, do not teach all of the elements of the claimed invention, and therefore, respectfully requests the rejection be withdrawn.

### Conclusion

Applicant believes that claims 1-20 are in a condition for allowance and respectfully request the Examiner reconsider and withdraw the rejection made in the outstanding Office Action. Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned so that they may be promptly resolved.

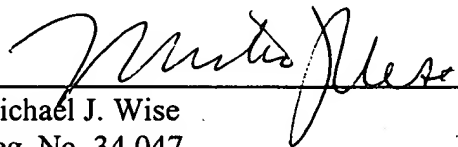
Respectfully submitted,

LYON & LYON LLP

Dated: \_\_\_\_\_

2/1/02

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**Marked Up Version to Show Amendments Pursuant to 37 CFR § 1.121:**

**IN THE SPECIFICATION:**

On page 6, line 19 of the specification, please delete the paragraph that begins with “A deposit...” and ends with “...namely HB9397” and replace the deleted paragraph with the following replacement paragraph:

A deposit of the monoclonal antibody DAS-1 (previously called 7E<sub>12</sub>H<sub>12</sub>, IgM isotype) has been made in the American Type Culture Collection, [12301 Parklawn Drive, Rockville, MD. 20852] 10801 University Blvd., Manassas, VA 20110-2209, and the deposited material has been accorded a specific accession number, namely HB9397.

Further, on page 21, line 8 of the specification, please delete the paragraph that begins with “Of the monoclonal...” and ends with “...ATCC#HB9397” and replace the deleted paragraph with the following replacement paragraph:

Of the monoclonal antibodies produced, the monoclonal antibody designated mAB DAS-1 gave the highest reactivity in the ELISA. The monoclonal antibody mAB DAS-1 was further purified by subcloning. The hybridoma secreting monoclonal antibody mAB DAS-1 is on deposit with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, where it was received April 16, 1987 and catalogued as ATCC #HB9397.

IN THE CLAIMS:

1. [Once Amended] An in vitro immunoassay method for diagnosing human colonic type gastric intestinal metaplasia which comprises the steps of:
  - (a) contacting a gastric tissue sample of a subject suspected of having human colonic type gastric intestinal metaplasia cells with the monoclonal antibody DAS-1, or a fragment thereof, which monoclonal antibody is produced by the hybridoma deposited under ATCC accession number HB 9397 and which reacts with human gastric intestinal metaplasia antigen; and
  - (b) detecting immunoreactivity between the gastric tissue and the monoclonal antibody, such immunoreactivity indicating a positive diagnosis of human colonic type gastric intestinal metaplasia.
2. [Once Amended] The method according to claim 1, wherein the human gastric intestinal metaplasia antigen is colon [epithial] epithelial specific protein.
3. [Once Amended] The method according to claim 1, wherein the antibody or fragment is directly [or indirectly] attached to a detectable label.
6. [Once Amended] The method according to claim 5, wherein the immunoperoxidase staining comprises:
  - (a) deparaffinizing the [intestinal] gastric tissue by heating;
  - (b) immersing the deparaffinized tissue in xylene;
  - (c) rehydrating the tissue in decreasing concentrations of alcohol;
  - (d) washing the rehydrated tissue in neutral PBS;
  - (e) reducing the aldehydes of the washed tissue of step (d);
  - (f) reacting the tissue with normal goat serum, the monoclonal antibody, biotinylated goat anti-mouse antibody and avidin-biotin-peroxidase complex;
  - (g) treating the reacted tissue with diaminobenzidine;
  - (h) washing the diaminobenzidine-treated tissue;
  - (i) staining the washed tissue of step (h) with hematoxylin, eosin or both; and

(o) examining the stained tissue under a microscope to detect the presence of immunoreactivity.

7. [Once Amended] The method according to claim 6, which further comprises the step of trypsinizing the gastric [intestinal] tissue after reducing the aldehydes in the tissue but before reacting the tissue with the goat serum, monoclonal antibody, biotinylated goat anti-mouse antibody and avidin-biotin-peroxidase complex.

9. [Once Amended] The method according to claim 1, further comprising the step of performing a negative control assay on a negative control sample to detect cells of human colonic type gastric intestinal metaplasia [cells] present in the negative control sample and comparing results of the assay in (b) with the results of the negative control assay, wherein the presence of human colonic type gastric intestinal metaplasia cells in the assay in (b) above the presence of human colonic type gastric intestinal metaplasia cells in the negative control assay indicates a positive diagnosis of human colonic type gastric intestinal metaplasia.

10. [Once Amended] The method according to claim 1, further comprising the step of performing a positive control assay on a positive control sample to detect human cells of colonic type gastric intestinal metaplasia [cells] present in the positive control sample.

11. [Once Amended] An in vitro immunoassay method for screening for human colonic type gastric intestinal metaplasia, [thereby indicating] wherein reactivity with DAS-1 is indicative of a predisposition for gastric carcinoma, which comprises the steps of:

- (a) contacting a gastric tissue sample of a subject suspected of having human colonic type gastric intestinal metaplasia cells with the monoclonal antibody DAS-1, or a fragment thereof, which monoclonal antibody is produced by the hybridoma deposited under ATCC accession number HB 9397 and which reacts with human gastric intestinal metaplasia antigen; and
- (b) detecting immunoreactivity between the gastric tissue and the monoclonal antibody, such immunoreactivity indicating a positive diagnosis of human colonic type gastric intestinal metaplasia.

12. [Once Amended] The method according to claim 11, wherein the human[,] gastric intestinal metaplasia antigen is colon [epithial] epithelial specific protein.

13. [Once Amended] The method according to claim 11, wherein the antibody or fragment is directly [or indirectly] attached to a detectable label.

16. [Once Amended] The method according to claim 15, wherein the immunoperoxidase staining comprises:

- (a) deparaffinizing the [intestinal] gastric tissue by heating;
- (b) immersing the deparaffinized tissue in xylene;
- (c) rehydrating the tissue in decreasing concentrations of alcohol;
- (d) washing the rehydrated tissue in neutral PBS;
- (e) reducing the aldehydes of the washed tissue of step (d);
- (f) reacting the tissue with normal goat serum, the monoclonal antibody, biotinylated goat anti-mouse antibody and avidin-biotin-peroxidase complex;
- (g) treating the reacted tissue with diaminobenzidine;
- (h) washing the diaminobenzidine-treated tissue;
- (i) staining the washed tissue of step (h) with hematoxylin, eosin or both; and examining the stained tissue under a microscope to detect the presence of immunoreactivity.

17. [Once Amended] The method according to claim 16, which further comprises the step of trypsinizing the gastric [intestinal] tissue after reducing the aldehydes in the tissue but before reacting the tissue with the goat serum, monoclonal antibody, biotinylated goat anti-mouse antibody and avidin-biotin-peroxidase complex.

19. [Once Amended] The method according to claim 16, further comprising the step of performing a negative control assay on a negative control sample to detect[-] cells of human colonic type gastric intestinal metaplasia [cells] present in the negative control sample and comparing results of the assay in (b) with the results of the negative control assay,

wherein the presence of human colonic type gastric intestinal metaplasia cells in the assay in (b) above the presence of human colonic type gastric intestinal metaplasia cells in the negative control assay indicates a positive diagnosis of human colonic type gastric intestinal metaplasia.

20. [Once Amended] The method according to claim 16, further comprising the step of performing a positive control assay on a positive control sample to detect human cells of colonic type gastric intestinal metaplasia [cells] present in the positive control sample.